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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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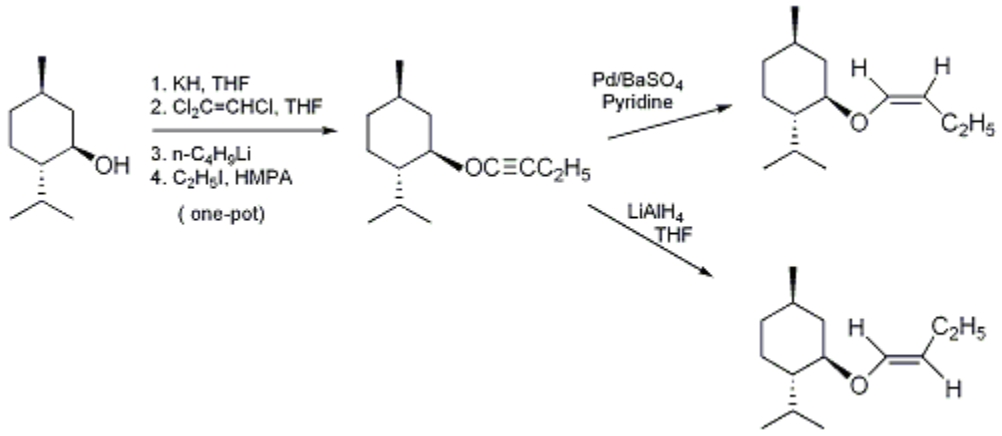
ACETYLENIC ETHERS FROM ALCOHOLS AND THEIR REDUCTION TO Z- AND E-ENOL ETHERS: PREPARATION OF 1-MENTHOXY-1-BUTYNE FROM MENTHOL AND CONVERSION TO (Z)- AND (E)-1-MENTHOXY-1-BUTENE

[[Cyclohexane, 2-(1-butynyloxy)-4-methyl-1-(1-methylethyl)-[1S-(1α,2β,4β)]-], and [[[Cyclohexane, 2-(1-butenyloxy)-4-methyl-1-(1-methylethyl)-, [1S-[1α,2β(Z),4β]]- and [1S-[1α,2β(E),4β]]-]



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1. Procedure

CAUTION! These transformations should be carried out in an efficient hood and only by persons familiar with the handling of air-sensitive and toxic materials. Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.

A. *1-Menthoxy-1-butyne*. A dry, 500-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is flushed with argon and charged with 13.2 g (115 mmol) of a 35% suspension of potassium hydride in mineral oil (Note 2). The mineral oil is removed by washing with pentane (3 × 30 mL) and the potassium hydride is suspended in 100 mL of anhydrous tetrahydrofuran (Note 3). The flask is capped with a rubber septum and is connected to a Nujol-filled bubbler by means of a syringe needle. A solution of 12.0 g (76.8 mmol) of (−)-menthol (Note 2) in 120 mL of anhydrous tetrahydrofuran is then added dropwise by syringe over 20 min. The mixture is stirred until hydrogen evolution is complete (ca. 20 min) and cooled to −50°C by means of an acetone-liquid nitrogen bath. A solution of trichloroethylene (7.58 mL, 84.4 mmol) (Note 3) in 75 mL of anhydrous tetrahydrofuran is added dropwise by syringe over 15 min, after which the reaction mixture is allowed to warm to room temperature and is stirred for 1 hr. The resulting brown solution is then cooled to −70°C and treated dropwise with 67.6 mL (169 mmol) of 2.5 M butyllithium in hexanes (Note 2). After the reaction mixture is stirred for 30 min at −70°C, it is warmed to −40°C over 30 min (Note 4) and treated dropwise with a solution of ethyl iodide (18.5 mL, 230 mmol) (Note 5) in 25 mL of hexamethylphosphoramide (Note 3), (Note 6). The solution is stirred at room temperature for 3 hr, whereupon it is quenched by slow addition of 15 mL of methanol and poured into 300 mL of cold aqueous saturated ammonium chloride. The phases are separated and the aqueous phase is extracted with pentane (3 × 200 mL). The combined organic phases are washed with water (4 × 150 mL), dried over sodium sulfate, and filtered. Concentration by rotary evaporation affords 17.1 g of dark brown oil, which is purified by bulb-to-bulb distillation (0.02 mm, oven temperature 70–90°C) to yield 14.9 g

(93%) of 1-menthoxy-1-butyne as a colorless oil (Note 7).

B. *(Z)-1-Menthoxy-1-butene*. A dry, 250-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is charged with 14.0 g (67.2 mmol) of 1-menthoxy-1-butyne, 0.7 g of 10% palladium on barium sulfate and 180 mL of pyridine (Note 8). The flask is capped with a rubber septum and by means of syringe needles is degassed and connected to a hydrogen-filled balloon. The mixture is stirred for 6 hr (Note 9), whereupon the hydrogen is replaced with argon, and the reaction mixture is filtered through a glass frit under water aspirator pressure. The filtrate is diluted with 300 mL of pentane and washed first with saturated copper sulfate solution (5 × 120 mL) and then with water (1 × 200 mL). The organic phase is dried over sodium sulfate and the solvent is removed by rotary evaporation to give 15.8 g of a yellow oil. Bulb-to-bulb distillation (0.02 mm, oven temperature 70–90°C) provides 12.7 g (90%) of (Z)-1-menthoxy-1-butene as a colorless oil (Note 10).

C. *(E)-1-Menthoxy-1-butene*. A dry, 500-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is flushed with argon and charged with 7.65 g (202 mmol) of lithium aluminum hydride (Note 11) and 325 mL of anhydrous tetrahydrofuran (Note 3) and then capped with a rubber septum and connected by means of a syringe needle to an argon-filled balloon. To the stirred slurry is added dropwise by syringe neat 1-menthoxy-1-butyne (14.0 g, 67.2 mmol), followed by 2 mL of tetrahydrofuran wash. The septum is replaced with a reflux condenser connected to an argon-filled balloon and the mixture is refluxed for 4 hr. After the flask is allowed to cool to room temperature, it is placed in an ice bath and the reaction mixture is quenched by the slow addition (*CAUTION!* (Note 12)) of 12.5 mL of aqueous 10 % sodium hydroxide, followed by 15.5 mL of water. The resulting mixture is stirred for 30 min, after which anhydrous sodium sulfate (ca. 60 g) is added and the solid material is removed by filtration through a 1-cm pad of Celite, which is then rinsed with diethyl ether (4 × 100 mL) . Concentration of the combined filtrates yields 14.7 g of a pale yellow oil, which is purified by filtration through a 4-cm (80-g) pad of silica gel pretreated with triethylamine (2.5% v/v, (Note 13)) using hexane as the eluant. Concentration gives 13.3 g (94%) of (E)-1-menthoxy-1-butene as a colorless oil (Note 14).

2. Notes

1. All glassware was flame-dried and allowed to cool in a desiccator before use.
2. Potassium hydride (35% in mineral oil) and (−)-menthol (99%) were purchased from the Aldrich Chemical Company, Inc., and butyllithium (2.5 M in hexanes) was obtained from Janssen Chimica.
3. Pentane and trichloroethylene were distilled from calcium chloride, tetrahydrofuran from the sodium ketyl of benzophenone, and hexamethylphosphoramide from calcium hydride under reduced pressure.
4. Quenching the reaction at this stage with methanol, followed by the work-up described below and bulb-to-bulb distillation (0.02 mm, oven temperature 60–80°C), gave 12.5 g (90%) of menthoxyacetylene as a colorless oil: $[\alpha]_D^{25}$ −74° (cyclohexane, *c* 0.76); IR (film) cm^{-1}: 3340, 2960, 2940, 2870, 2150, 1450, 1370, 1100, 940, 890, 840; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.68–1.54 (m, 5 H; CH and CH_2), 0.81 (d, 3 H, J = 6.9, CH_3), 0.90 (d, 3 H, J = 7.0, CH_3), 0.94 (d, 3 H, J = 6.4, CH_3), 1.49 (s, 1 H, C≡CH), 1.57–1.74 (m, 2 H), 2.00–2.33 (m, 2 H), 3.83 (app td, 1 H, J = 10.9, 4.5, CH-O-); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 16.3 (CH_3), 20.5 (CH_3), 22.0 (CH_3), 23.3 (CH_2), 25.9 (CH), 27.1 (C), 31.6 (CH), 33.9 (CH_2), 39.4 (CH_2), 46.7 (CH), 88.2 (CH), 89.7 (CH); mass spectrum (chemical ionization), m/e 181 (M^+ + 1, 5%), 156 (100%), 139 (58%); analytical TLC (pentane): Rf 0.54 (single spot). Proton NMR confirmed the complete absence (<1%) of menthol. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: 79.72; H, 10.98.
5. Ethyl iodide (99%) was purchased from Prolabo (Paris, France) and was washed with saturated aqueous sodium thiosulfate solution, dried over anhydrous sodium sulfate and then sodium metal, and distilled prior to use.
6. Dimethylpropyleneurea (75 mL) can be used in place of hexamethylphosphoramide; however, a small amount (5–10%) of menthoxyacetylene contaminates the final product.
7. Data for 1-menthoxy-1-butyne are as follows: $[\alpha]_D^{25}$ −78° (cyclohexane, *c* 0.69); IR (film) cm^{-1}: 2950, 2925, 2870, 2280, 1460, 1390, 1370, 1250, 1230, 1210, 980, 950, 910, 840; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.75–1.20 (m, 3 H, CH and CH_2), 0.80 (d, 3 H, J = 6.9, CH_3), 0.89 (d, 3 H, J = 7.1, CH_3), 0.93 (d, 3 H, J = 6.4, CH_3), 1.08 (t, 3 H, J = 7.5, CH_2CH_3), 1.27–1.51 (m, 2 H), 1.64 (br d, 2 H), 2.11 (q, 2 H, J = 7.5, CH_2CH_3), 2.12–2.25 (m, 2 H), 3.69 (app td, 1 H, J = 10.9, 4.5, CHO); ^{13}C NMR (50.3 MHz,

$CDCl_3$) δ: 11.0 (CH_2), 15.1 (CH_3), 16.2 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 23.2 (CH_2), 25.7 (CH), 31.5 (CH), 34.0 (CH_2), 39.6 (2C: C and CH_2), 46.8 (CH), 86.9 (CH), 87.4 (C); mass spectrum (chemical ionization), m/e 209 ($M^+ + 1$, 4%), 156 (100%), 139 (26%); analytical TLC (pentane): R_f 0.54 (single spot). Proton NMR indicated a complete absence (<1%) of both menthol and menthoxyacetylene. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.70; H, 11.55.

8. 10% Palladium on barium sulfate was purchased from Fluka Chemie AG and pyridine (99.5%) was obtained from Chimie-Plus Laboratories (St.-Priest, France) and dried over calcium hydride before use.

9. The reaction was followed by IR analysis of worked-up aliquots (disappearance of band at 2280 cm^{-1}).

10. Data for (Z)-1-menthoxy-1-butene are as follows: $[\alpha]_D^{25}$ −18° (cyclohexane, *c* 0.11); IR (film) cm^{-1}: 3030, 2970, 2920, 2870, 1660, 1460, 1380, 1350, 1250, 1140, 1110, 1090, 1070, 1050; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.72–1.08 (m, 3 H, CH and CH_2), 0.80 (d, 3 H, J = 7.0, CH_3), 0.92 (d, 3 H, J = 7.1, CH_3), 0.93 (d, 3 H, J = 6.5, CH_3), 0.97 (t, 3 H, J = 7.5, CH_2CH_3), 1.22–1.46 (m, 2 H), 1.56–1.70 (m, 2 H), 1.85–2.21 (m, 4 H), 3.35 (app td, 1 H, J = 10.7, 4.3, CHOCH=CH), 4.32 (app q, 1 H, J = 7.1, OCH=CH), 5.97 (d, 1 H, J = 6.2, -OCH=CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 14.6 (CH_3), 16.5 (CH_3), 17.5 (CH_2), 20.7 (CH_3), 22.2 (CH_3), 23.6 (CH_2), 25.8 (CH), 31.5 (CH), 34.5 (CH_2), 41.6 (CH_2), 47.9 (CH), 81.3 (CH), 108.2 (CH), 143.6 (CH); mass spectrum (electron impact) m/e 210 (M^+, 14%), 138 (32%), 83 (100%); analytical TLC (pentane): R_f 0.59 (major spot). Proton NMR indicated a complete absence (<1%) of menthol, menthoxybutyne, and menthoxybutane, but the presence of ca. 3% of the E -isomer. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.84; H, 12.55.

11. Lithium aluminum hydride (95+%) was purchased from Janssen Chimica. Lesser amounts led to incomplete reaction under the stated conditions.

12. *CAUTION! Quenching should be performed very carefully as a rapid, exothermic evolution of hydrogen occurs during the initial phase. Flushing with argon throughout the quenching is recommended.* Toward completion of the sodium hydroxide addition, a thick slurry is produced, which makes stirring difficult. This difficulty is alleviated, however, upon the addition of water.

13. Silica gel (70-230 mesh) was treated with triethylamine (2.5% v/v) and then shaken to achieve homogeneity.

14. Data for (E)-1-menthoxy-1-butene are as follows: $[\alpha]_D^{25}$ −37° (cyclohexane, *c* 0.80); IR (neat) cm^{-1}: 2960, 2910, 2860, 1670, 1650, 1450, 1180, 1140, 920; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.71–1.08 (m, 3 H, CH and CH_2), 0.75 (d, 3 H, J = 7.0, CH_3), 0.87 (d, 3 H, J = 7.1, CH_3), 0.89 (d, 3 H, J = 6.5, CH_3), 0.94 (t, 3 H, J = 7.4, CH_2CH_3), 1.19–1.46 (m, 2 H), 1.54–1.70 (m, 2 H), 1.90 (app quint d, 2 H, J = 7.3, 1.3), 1.96–2.21 (m, 2 H), 3.36 (app td, 1 H, J = 10.6, 4.3, CHOCH=CH), 4.88 (dt, 1 H, J = 12.3, 7.0, OCH=CH), 6.06 (dt, 1 H, J = 12.3, 1.3, OCH=CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 15.2 (CH_3), 16.3 (CH_3), 20.8 (CH_3), 21.0 (CH_2), 22.2 (CH_3), 23.4 (CH_2), 25.7 (CH), 31.5 (CH), 34.4 (CH_2), 41.1 (CH_2), 47.8 (CH), 80.0 (CH), 107.5 (CH), 144.8 (CH); mass spectrum (electron impact), m/e 210 (M^+, 4%), 83 (100%), 69 (40%); analytical TLC (pentane): R_f 0.53 (single spot). Proton NMR confirmed the complete absence (<1%) of menthol, menthoxybutyne, menthoxybutane, and the Z-isomer. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.91; H, 12.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The conversion of menthol to 1-menthoxy-1-butyne described in Part A illustrates an efficient, one-pot preparation of acetylenic ethers from alcohols that is relatively inexpensive and requires only common reagents and standard laboratory equipment. It is substantially higher-yielding and more direct and generally applicable than other available approaches to these versatile[2] compounds, which generally involve base treatment of haloalkenyl ethers, dihaloalkyl ethers, haloacetals, or related compounds.[2] The conversion in this procedure is an optimized example of a method that has previously been applied with success to a wide range of secondary alcohols.[3] Several primary alcohols have also been transformed to acetylenic ethers through this method.[4]

Parts B and C exemplify efficient procedures for the stereoselective reduction of acetylenic ethers to

the corresponding Z- and E-enol ethers, synthetically useful intermediates.[5] These procedures, which are optimized versions of previously described methods,[3,6] also require only common reagents and standard laboratory equipment. Alternatively, acetylenic ethers can be converted stereoselectively to E-enol ethers under Birch conditions[3] and to Z- (or E-) enol ethers with Red-Al.[7]

Other known methods for preparing O-alkyl enol ethers include, most notably, alcohol elimination from acetals, double bond isomerization in allylic ethers, reduction of alkoxy enol phosphates, and phosphorane-based condensation approaches.[5] These methods, however, suffer from poor stereoselectivity, low yields, or lack of generality, if not a combination of these drawbacks.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

sodium ketyl of benzophenone

(−)-Menthol

(Z)- AND (E)-1-MENTHOXY-1-BUTENE

[Cyclohexane, 2-(1-butynyloxy)-4-methyl-1-(1-methylethyl)-[1S-(1α,2β,4β)]-]

[[[Cyclohexane, 2-(1-butenyloxy)-4-methyl-1-(1-methylethyl)-, [1S-[1α,2β(Z),4β]]- and [1S-[1α,2β(E),4β]]-

calcium chloride (10043-52-4)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

copper sulfate (7758-98-7)

cyclohexane (110-82-7)

barium sulfate (7727-43-7)

pyridine (110-86-1)

sodium (13966-32-0)

palladium (7440-05-3)

Pentane (109-66-0)

menthol (15356-60-2)

Ethyl iodide (75-03-6)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

trichloroethylene (79-01-6)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

1-Adamantanol (768-95-6)

hexamethylphosphoric triamide,
hexamethylphosphoramide (680-31-9)

2-cyclohexylethanol (4442-79-9)

decanol (112-30-1)

potassium hydride (7693-26-7)

dimethylpropyleneurea (7226-23-5)

1-Menthoxy-1-butyne (108266-28-0)

(E)-1-MENTHOXY-1-BUTENE,
(Z)-1-Menthoxy-1-butene (107941-62-8)

menthoxyacetylene

menthoxybutyne

menthoxybutane

adamantyloxyacetylene